Title: Classification criteria for pars planitis

Suggested running title: Pars planitis

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ABSTRACT

Purpose: To determine classification criteria for pars planitis

Design: Machine learning of cases with pars planitis and 4 other intermediate uveitides.

Methods: Cases of intermediate uveitides were collected in an informatics-designed preliminary data base, and a final data base was constructed of cases achieving supermajority agreement on the diagnosis, using formal consensus techniques. Cases were split into a learning set and a validation set. Machine learning using multinomial logistic regression was used on the learning set to determine a parsimonious set of criteria that minimized the misclassification rate among the intermediate uveitides. The resulting criteria were evaluated on the validation set.

Results: Five hundred eighty-nine of cases of intermediate uveitides, including 226 cases of pars planitis, were evaluated by machine learning. The overall accuracy for intermediate uveitides was 99.8% in the learning set (95% confidence interval [CI] 98.7, 100) and 99.3% in the validation set (95% CI 96.1, 99.9). Key criteria for pars planitis included unilateral or bilateral intermediate uveitis with either 1) snowballs in the vitreous or 2) snowbanks on the pars plana. Key exclusions included: 1) multiple sclerosis, 2) sarcoidosis, and 3) syphilis. The misclassification rates for pars planitis were 0 % in the learning set and 1.7% in the validation set, respectively.

Conclusions: The criteria for pars planitis had a low misclassification rate and appeared to perform sufficiently well for use in clinical and translational research.

PRECIS

Using a formalized approach to developing classification criteria, including informatics-based case collection, consensus-technique-based case selection, and machine learning, classification criteria for pars planitis were developed. Key criteria included intermediate uveitis with either vitreous snowballs or snowbanks. Exclusions included multiple sclerosis, sarcoidosis, and syphilis. The resulting criteria had a low misclassification rate.

Intermediate uveitis refers to a class of uveitic diseases characterized by inflammation predominantly in the vitreous and an absence of retinitis and choroiditis.[1,2] Intermediate uveitides may be associated with infections, such as Lyme disease or syphilis, or with systemic diseases, particularly sarcoidosis and multiple sclerosis, or it may occur as an isolated, presumably immune-mediated, ocular disorder of unknown etiology.[1] Pars planitis represents a subset of intermediate uveitis characterized by fibro-inflammatory material overlying the pars plana and peripheral retina ("snowbanks").[1,2] Initially noted by Schepens[3] in 1950 and termed "peripheral uveitis", the features of what is now termed pars planitis were described nearly simultaneously in 1960 by Welch et al[4] and Brockhurst et al[5]. Also termed cyclitis by Hogan and Kimura,[6] the name "pars planitis" was coined by Welch et al[4], and pars planitis has remained as the most commonly used term for this intermediate uveitic disease. Although snowbanks have been considered the traditional hallmark of pars planitis, a similar uveitic disorder occurs as an intermediate uveitis without snowbanks or snowballs (fibro-inflammatory debris typically in the inferior vitreous), which now is termed intermediate uveitis, non-pars planitis type,[2] and which also could be considered an "undifferentiated intermediate uveitis". Case series which included both pars planitis and non-pars planitis types of intermediate uveitis have made interpretation of the literature more difficult.[7] In 2005, the Standardization of Uveitis Nomenclature (SUN) Working Group at a consensus meeting agreed that the term pars planitis should apply to cases of non-infectious intermediate uveitis with vitritis and either inferior vitreous inflammatory condensates ("snowballs") or pars plana "snowbanks", unassociated with a systemic disease, and that it should be distinguished from intermediate uveitis, non-pars planitis type.[2] Furthermore, the group recognized that pars planitis may have peripheral retinal vascular sheathing and non-perfusion (more easily seen on wide-field fluorescein angiography) but should not have posterior pole or mid-peripheral occlusive retinal vasculitis.[2]

Given the definitional variation in the disease, its frequency in referral center case series has been reported to vary from 2.4 to 15.4% of uveitis cases,[8,9] and its incidence has been

estimated at 2.08/100,000/year.[10] Structural complications of intermediate uveitides include macular edema, epiretinal membrane formation, and uncommonly retinal neovascularization of either the disc or the snowbank. Anterior chamber inflammation typically is mild and the eye is not acutely inflamed. Presenting symptoms typically are either floaters or blurred vision, most often due to macular edema.[10-12]

The SUN Working Group is an international collaboration, which has developed classification criteria for 25 of the most common uveitides using a formal approach to development and classification.[2, 13-17] Among the intermediate uveitides studied was pars planitis.

Methods

The SUN Developing Classification Criteria for the Uveitides project proceeded in four phases as previously described: 1) informatics, 2) case collection, 3) case selection, and 4) machine learning.[13-15,17]

Case collection and case selection. Information was entered into the SUN preliminary database by the 76 contributing investigators for each disease as previously described.[15,17] Cases in the preliminary database were reviewed by committees of 9 investigators for selection into the final database.[15,17] Because the goal was to develop classification criteria,[16] only cases with a supermajority agreement (>75%) that the case was the disease in question were retained in the final database (i.e. were "selected").[17]

Machine learning. The final database then was randomly separated into a learning set (~85% of cases) and a validation set (~15% cases) for each disease as described in the accompanying article.[17] Machine learning was used on the learning set to determine criteria that minimized misclassification. The criteria then were tested on the validation set; for both the learning set and the validation set, the misclassification rate was calculated for each disease. For pars planitis, the diseases against which it was evaluated were: multiple sclerosis (MS)-associated intermediate uveitis; intermediate uveitis, non-pars planitis type (undifferentiated

intermediate uveitis); sarcoidosis-associated intermediate uveitis, and syphilitic intermediate uveitis. Too few cases of Lyme disease-associated uveitis were collected in the data base for analysis by machine learning.

Comparison of cases with and without snowbanks. Comparison of the characteristics of cases with and without snowbanks was performed with the chi-square test for categorical variables or the Fisher's exact test when the count of a variable was less than 5. Continuous variables were summarized as medians and compared with the Wilcoxon rank sum test. For characteristics with multiple categorical grades, values above and below the median were compared. P-values are nominal and two-sided.

The study adhered to the principles of the Declaration of Helsinki. Institutional Review Boards (IRBs) at each participating center reviewed and approved the study; the study typically was considered either minimal risk or exempt by the individual IRBs.

Results

Three hundred eight cases of pars planitis were collected, and 226 (73%) achieved supermajority agreement on the diagnosis during the "selection" phase and were used in the machine learning phase. These cases of pars planitis were compared to 363 cases of other intermediate uveitides, including 112 cases multiple sclerosis-associated intermediate uveitis, 114 cases of intermediate uveitis, non-pars planitis type, 52 cases of sarcoidosis-associated intermediate uveitis, and 85 cases of syphilitic intermediate uveitis. The details of the machine learning results for these diseases are outlined in the accompanying article.[17] The characteristics at presentation to a SUN Working Group Investigator of cases with pars planitis are listed in Table 1. A comparison of cases with and without snowbanks is listed in Table 2. The only significant difference between those with snowbanks and those without snowbanks was that those with snowbanks were younger. The criteria developed after machine learning are listed in Table 3. The overall accuracy for intermediate uveitides was 99.8% in the learning set (95% confidence interval [CI] 98.7, 100) and 99.3% in the validation set (95% CI 96.1,

99.2).[17] The misclassification rate for pars planitis in the learning set was 0% and in the validation set 1.7%.

Discussion

The classification criteria developed by the SUN Working Group for pars planitis have a low misclassification rate, indicating good discriminatory performance against other intermediate uveitides.

The distinctive feature of pars planitis classically has been the presence of inferior snowbanks (Figure 1). Histopathologic examination has demonstrated fibro-glial or fibro-vascular proliferation with non-granulomatous inflammation composed of mononuclear inflammatory cells, lymphocytic cuffing and mural infiltration of retinal venules, and hyperplastic non-pigmented epithelium of the pars plana.[18,19] Because the SUN definition of pars planitis[2] allowed inclusion of cases with snowballs but not snowbanks, we compared cases with and without snowbanks. The only significant difference detected was the younger age at presentation of those with snowbanks. Whether this difference represents a more exuberant response to the same disease among younger patients or a different pathogenetic mechanism cannot be determined at this time. One study suggested that the course of pars planitis in childhood may be different than that in adults with a higher rate of sustained, drug-free remissions,[20] but this impression needs to be confirmed. Long-term follow-up studies of patients with and without snowbanks are needed and may help determine if these two subsets should continue to be considered within the spectrum of the same disorder or separate ones. However, at this time, the criteria include both subsets in the term “pars planitis”;[2] it would seem prudent that studies of patients with pars planitis report and evaluate the two subsets “with and without snowbanks”, in order to evaluate any differences.

Ultra-wide-field angiography has demonstrated the presence of peripheral vascular cuffing, leakage, and non-perfusion in patients with pars planitis.[21-23] These findings are distinct from the posterior pole and mid-peripheral occlusive retinal vasculitides, such as that seen in

Behçet disease, and pars planitis should be diagnosed separately and not be lumped with the more severe occlusive retinal vasculitides.

Pars planitis has been associated with the HLA type HLA-DR2, and with its split antigen HLA-DR15 with relative odds in the 3 to 5 range.[12,25] Although there is an association, the positive predictive value[25] of these antigens is poor owing to the high population prevalence of the genes. Furthermore, HLA-DR2 and DR15 are risk factors for multiple sclerosis,[12] rendering them unhelpful for distinguishing between pars planitis and MS-associated uveitis.

Multiple sclerosis has been associated with intermediate uveitis,[11,12] but at this time it is considered distinct from pars planitis without MS.[2] Nevertheless, the two disorders may have overlapping features, including snowballs and/or snowbanks in some patients with MS-associated uveitis.[26] Furthermore, patients presenting with pars planitis without MS have been estimated to have a risk of developing MS of ~2 to 4%/year,[11,12] so that neuro-imaging to exclude multiple sclerosis is likely to have a low yield and is not routinely recommended.[27] Multiple sclerosis should be excluded on clinical grounds, beginning with the absence of relevant neurological lesions or a history of such lesions, and using the McDonald criteria.[28] As such, some cases initially diagnosed as having pars planitis may have their diagnosis changed with follow-up and the development of MS. Peripheral vascular changes have been reported as a risk factor for subsequent development of MS,[11] and the prevalence of peripheral vascular sheathing and/or leakage was greater in cases with MS-associated uveitis,[17,26] but not sufficiently so to be of diagnostic utility.[17]

The presence of any of the exclusions in Table 2 suggests an alternate diagnosis, and the diagnosis of pars planitis should not be made in their presence. In prospective studies many of these tests will be performed routinely, and the alternative diagnoses excluded. However, in retrospective studies based on clinical care, not all of these tests may have been performed. Hence the presence of an exclusionary criterion excludes pars planitis, but the absence of such testing does not always exclude the diagnosis of pars planitis if the criteria for

the diagnosis are met. Nevertheless, because of the overlapping features of sarcoidosis-associated intermediate uveitis, including snowballs, a reasonable attempt should be made to exclude sarcoidosis, including at a minimum chest imaging, for all cases of pars planitis.[29]

The type of uveitis most often seen with Lyme disease is an atypical intermediate or anterior and intermediate uveitis, but disease indistinguishable from pars planitis has been described.[30,31] Lyme uveitis is sufficiently uncommon that we were unable to collect a sufficient number of cases for analysis. Nevertheless, it would be prudent to exclude Lyme disease in cases of intermediate uveitis from Lyme disease endemic areas or in Lyme disease exposed patients. However, in Lyme disease non-endemic regions, there appears to be little value to screening for Lyme disease.[32]

Classification criteria are employed to diagnose individual diseases for research purposes.[16] Classification criteria differ from clinical diagnostic criteria, in that although both seek to minimize misclassification, when a trade-off is needed, diagnostic criteria typically emphasize sensitivity, whereas classification criteria emphasize specificity,[16] in order to define a homogeneous group of patients for inclusion in research studies and limit the inclusion of patients without the disease in question that might confound the data. The machine learning process employed did not explicitly use sensitivity and specificity; instead it minimized the misclassification rate. Because we were developing classification criteria and because the typical agreement between two uveitis experts on diagnosis is moderate at best,[15] the selection of cases for the final database ("case selection") included only cases which achieved supermajority agreement on the diagnosis. As such, some cases which clinicians would diagnose with pars planitis will not be so classified by classification criteria. The selection of cases during case selection of cases which achieved supermajority agreement on the diagnosis for inclusion in the final data base was used because we were developing classification criteria.

In conclusion, the criteria for pars planitis outlined in Table 3 appear to perform sufficiently well for use as classification criteria in clinical research.[16,17]

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297 **Table 1. Characteristics of Cases with Pars Planitis**

Characteristic	Result
Number cases	226
Demographics	
Age, median, years (25^{th} 75^{th} percentile)	22 (11, 36)
Gender (%)	
Men	48
Women	52
Race/ethnicity (%)	
White, non-Hispanic	72
Black, non-Hispanic	5
Hispanic	6
Asian, Pacific Islander	3
Other	6
Missing	8
Uveitis History	
Uveitis course (%)	
Acute, monophasic	2
Acute, recurrent	2
Chronic	87
Indeterminate	9
Laterality (%)	
Unilateral	15
Unilateral, alternating	0
Bilateral	85
Ophthalmic examination	
Keratic precipitates (%)	
None	83
Fine	15
Round	2
Stellate	0
Mutton Fat	0
Other	0
Anterior chamber cells (%)	
Grade 0	44
½+	27
1+	19
2+	9
3+	1
4+	0
Hypopyon (%)	0
Anterior chamber flare (%)	
Grade 0	75
1+	21
2+	3
3+	1
4+	0
Iris (%)	

Normal	88
Posterior synechiae	12
Sectoral iris atrophy	0
Patchy iris atrophy	0
Diffuse iris atrophy	0
Heterochromia	0
Intraocular pressure (IOP), involved eyes	
Median, mm Hg (25^{th}, 75^{th} percentile)	14 (12, 17)
Proportion patients with IOP>24 mm Hg either eye (%)	4
Vitreous cells (%)*	
Grade 0	4
½+	8
1+	35
2+	39
3+	13
4+	1
Vitreous haze (%)*	
Grade 0	31
½+	15
1+	27
2+	23
3+	3
4+	1
Vitreous snowballs†	83
Pars plana snowbanks†	44
Peripheral retinal vascular sheathing or leakage	25
Macular edema	43

*All cases had either vitreous cells or haze; only one case had haze without evident cells. †All cases snowballs or snowbanks; 124 cases had snowballs without snowbanks.

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Table 2. Characteristics of Cases with Pars Planitis with and without Snowbanks

Characteristic	Patients with Snowbanks	Patients without Snowbanks	P-value
Number cases	104	124	
Demographics			
Age, median, years (25th 75th percentile)	19 (10, 30)	39 (27, 52)	<0.001
Gender (%)			0.68
Men	50	47	
Women	50	53	
Race/ethnicity (%)			0.25
White, non-Hispanic	70	73	
Black, non-Hispanic	4	6	
Hispanic	6	6	
Asian, Pacific Islander	2	3	
Other	4	5	
Missing	14	7	
Uveitis History			
Uveitis course (%)			0.54
Acute, monophasic	1	3	
Acute, recurrent	1	3	
Chronic	87	86	
Indeterminate	11	8	
Laterality (%)			0.92
Unilateral	16	15	
Bilateral	84	85	
Ophthalmic examination			
Keratic precipitates (%)			0.31
None	85	80	
Fine	14	18	
Round	1	2	
Anterior chamber cells (%)*			0.17
Grade 0	50	40	
Grade ½+ or greater	50	60	
Anterior chamber flare (%)*			0.14
Grade 0	80	72	
Grade 1+ or greater	20	28	
Iris (%)			0.07
Normal	92	84	
Posterior synechiae	8	16	
Intraocular pressure (IOP), involved eyes			
Median, mm Hg (25th, 75th percentile)	14 (12, 17)	14 (12, 17)	1.00
Vitreous cells (%)*			0.17
Grades 0 to 1+	42	51	
Grades 2+ or greater	58	49	
Vitreous haze (%)*			0.12
Grades 0 to ½+	52	41	
Grades 1+ or greater	48	59	
Vitreous snowballs†	71	100	

Pars plana snowbanks†	100	0	-
Peripheral retinal vascular sheathing or leakage	23	27	0.51
Macular edema	38	48	0.15

*Analyses compare values above and below the median value. †Presence or absence of snowbanks = defining characteristic of the two subsets; cases without snowbanks required to have snowballs to be classified as having pars planitis.

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301 **Table 3. Classification Criteria for Pars Planitis**

Criteria
1. Evidence of intermediate uveitis a. vitreous cells AND/OR vitreous haze b. if anterior chamber cells are present, anterior chamber inflammation severity less than vitreous severity c. no evidence of retinitis or choroiditis d. no retinal vascular occlusion in posterior pole & mid-periphery* AND 2. Evidence of pars planitis a. vitreous snowballs OR b. pars plana snowbanks
Exclusions
1. Multiple sclerosis, defined by the McDonald criteria[28] 2. Positive serology for syphilis using a treponemal test 3. Evidence of sarcoidosis (either bilateral hilar adenopathy on chest imaging or tissue biopsy demonstrating non-caseating granulomata) 4. Positive serology for Lyme disease, either IgG or IgM (e.g. positive ELISA AND Western blot with requisite number of bands for assay used)

*Peripheral retinal non-perfusion on wide-field angiography is compatible with pars planitis diagosis.

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FIGURE LEGENDS

Figure 1. Pars plana snowbank in a patient with pars planitis.